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CONGESTIVE SPLENOMEGALY

Case Report No. 77

Dr. Ralph Stiller L. S. 46–6809

L. S., a 2½ year old white female, was admitted to Children's Hospital on July 22, 1946 with a chief complaint of an "enlarged spleen." One month prior to admission she had a cold and on routine physical examination by a Navy physician in Honolulu a greatly enlarged spleen was noted. Two blood counts done at that time showed a leukopenia in the neighborhood of 2,500 white cells. The family was transferred to the Washington area for diagnosis and treatment of the child. She had been perfectly well since birth and the family feels she is quite well now.

The mother's pregnancy and labor and the child's development had been uneventful. With the exception of occasional colds and sore throats she had never been ill. Past history failed to reveal any evidence of malaria, her stay in Honolulu having only been two months. Her appetite recently had been quite good. She was afebrile prior to admission.

On physical examination the only finding of note was the greatly enlarged spleen that filled the left abdomen, dipping below the iliac crest. The splenic notch could be felt easily. The organ was quite mobile and could be visualized by pressing it anteriorly against the abdominal wall.

Laboratory findings included: Bleeding time 1¾ minutes; coagulation time 6 minutes and on another occasion 3 minutes; prothrombin time was 94% of normalcy; icterus index 3 units; blood cholesterol 120 mgm.%; fragility test was normal; Wassermann negative; febrile agglutinations negative; malaria smear negative and urinalysis on two occasions was negative.

The buffy-coat showed the same differential as the blood count and bone marrow puncture showed a diminution of platelets and megakarocytes. Many blood counts were taken and they can best be shown in the accompanying chart.

Roentgen examination of the skull and long bones revealed no abnormality except for transverse lines of increased density at the epiphyseal ends of the metaphyses of the long bones. This was associated with slight broadening of the ends of the long bones. Fluoroscopic examination after a barium swallow failed to reveal any esophageal varices. Some displacement of the stomach to the right by the enlarged spleen was noted.

The course in the hospital was uneventful and with the establishment of the diagnosis of congestive splenomegaly, splenectomy was decided upon. This was postponed for about a week when the child developed an upper respiratory infection with some interstitial pneumonitis. Treated with

penicillin, she made an uneventful recovery. She was transfused pre and post-operatively.

At operation a grossly enlarged spleen and several accessory spleens were removed. There was no evidence of portal vein pathology and the liver

CHART 1. Course of L. S. pre- and post-splenectomy

DATE	HGB.	RBC	WBC	NEUTRO-PHILS	PLATELETS	COURSE
6/21		3.2M	2,200	40		
7/23	9.5	3.5	4,100	31	40,000	
7/25	11.5	4.0	6,100	30	90,000	Bone Marrow Biopsy.
7/30						Trans. 225 cc. blood. Reaction —Temp. 105 degrees.
8/1						Low grade fever, cough. ROMCA, Mild Pharyngitis. *Treat.* Penicillin 15,000 u. q3h. Trans. 200 cc. whole blood. Reaction—Temp. 102 degrees.
8/3						Interstitial Pneumonitis.
8.4	12.5	3.6	2,300	14	40,000	
8/5						Afebrile. Disc. Penicillin.
8/9	13	4.2	5,300	47	100,000	
8/10	15.5	6.3	14,000	88	350,000	Splenectomy. Trans. 375 cc. blood, 100 cc. Saline.
8/12	15	5.3	12,000	66	275,000	Mild U.R.I.
8/13		5.2			520,000	BOMCA. Penicillin 15,000 u. q3h.
8/15	14.5	5.5	8,600	50	594,000	
8/16						Disc. Penicillin.
8/17		5.6	9,200	27	500,000	
					715,000	
					300,000	
8/19	13	5.0	6,100	33	576,000	
					700,000	
8/21		5.1			160,000	
8/23	14	5.0	6,400	32	300,000	Discharged from Hospital.
8/29	13.5	5.5	10,900	40	230,000	
9/5	12.5	5.0	9,000	22	290,000	Follow-up at home.
9/17	12.5	4.5	7,500	18	234,000	

appeared normal. Post-operatively there was a slight febrile rise to 101° that subsided in 3 days. As can be seen by the accompanying chart (Table 2) there was a marked rise of all blood elements following splenectomy. The platelets rose to 700,000 during the first week postoperatively but gradually declined to normal levels. Heparinization was considered and would have been instituted if the extreme rise had been sustained. She recovered well and left the hospital 11 days post-operatively.

The pathological report of the spleen follows: *Gross*—The spleen weighed 157 gms. and measured 11 x 7 x 4 cm. The external surface was smooth and of a dark purple color. There was no adhesion to the adjacent organs. The cut surface was smooth, firm and of a bright red color. *Microscopic*—Sections of the spleen showed splenic tissue with unusually well defined follicles, the reticulo-endothelial structure being quite hyperplastic, the lymphoid elements reduced to a narrow zone about its periphery. In general the endothelial framework was prominent due to the striking paucity of the cellular elements of the pulp.

Sections of the splenic vein showed no significant pathological condition.

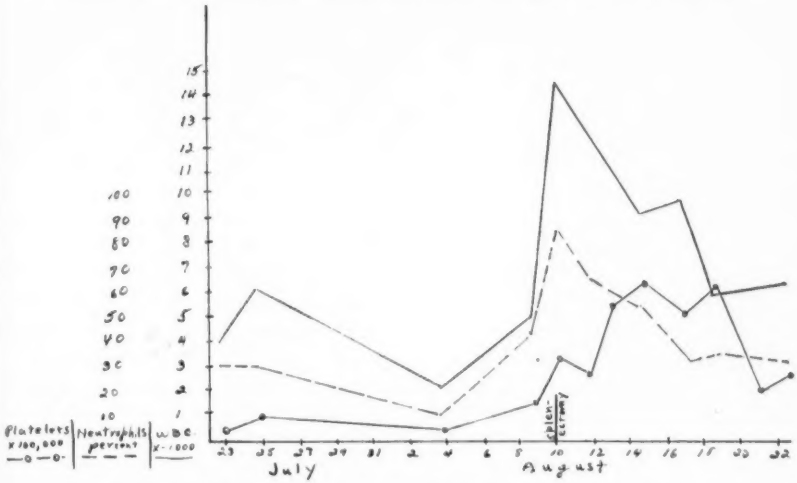

CHART 2. Illustrating the rise in the formed elements of the blood following splenectomy

DISCUSSION

Dr. Ralph Stiller: The diagnosis of congestive splenomegaly or Banti's Disease as it has been called was arrived at in this case by a process of exclusion that is typical of the method that must be used before such a rather unsatisfactory diagnosis can be entertained. Gretzel in 1866 coined the name splenic anemia to describe enlargement of the spleen associated with anemia, and in 1882 Banti combined this poorly understood disease with the cirrhosis of the liver that was often in association with it and thus described the complex that now bears his name. But with the advance in hematological knowledge various other entities have been split off from the original group which constantly becomes smaller remaining always as the wastebasket diagnosis in these cases; the criteria are chronic splenomegaly,

a slowly progressive anemia, leukopenia with a relative neutropenia, and hemorrhagic phenomena in the absence of any other findings that would help to classify the case more thoroughly.

Diamond has suggested the name congestive splenomegaly for this clinical group and has further subdivided them into two groups on the basis of apparent etiology. He states "congestion and stasis in the spleen produced either by some abnormality within the organ or in the spleno-portal circulation may result in a symptom complex consisting of splenomegaly, anemia, and associated disturbances. The signs and symptoms depend on the point of obstruction, collateral circulation and functional disturbances in affected organs, chiefly spleen which may affect the bone marrow and produce anemia, leukopenia and thrombopenia."

Current classification includes: Type I—Congestive splenomegaly secondary to obstruction of the portal or splenic vein: This manifests itself suddenly with hematemesis in a child of good health. There is a slightly enlarged spleen which gradually enlarges between bouts of hematemesis and shrinks a little just after an attack. After several years a permanent splenomegaly is present. Pathologically the spleen is large, firm and fibrotic with little red pulp, distended sinuses and compression of the Malpighian corpuscles. Associated with these attacks are left upper quadrant abdominal pain, melena and the classical symptoms of shock due to hemorrhage. The blood count resembles that following massive hemorrhage and eventually stabilizes with the picture of a microcytic hypochromic anemia. There is a leukopenia of 5,000 or less and a relative lymphocytosis. Platelets may be low normal and the disease at certain stages may simulate idiopathic thrombocytopenic purpura. X-ray of the esophagus may show varices. The prognosis may be good if an efficient collateral circulation is established.

Type II—Congestive splenomegaly secondary to intrinsic factors in the spleen: This type has an insidious onset with weakness, fatigue, anorexia and loss of weight. Hematemesis and its associated symptoms may come late in the disease as may petechiae and ecchymosis. There is a constant enlargement of the spleen. Laboratory examinations on the blood reveal a moderate degree of hypochromic, microcytic anemia with a leukopenia of 1,500–5,000, a relative and absolute neutropenia, and a thrombocytopenia. The bleeding time may be prolonged.

The diagnosis of Type II is made by exclusion, all the causes of splenomegaly being ruled out. Prior to the use of splenectomy as therapy, this type was marked by a slow progression with ascites, hematemesis and death. Surgery has resulted in an improvement of the anemia, leukopenia and thrombopenia. It is not known as yet what permanent effect this will have in the eventual outcome of the disease though figures tend to show a

fairly high percentage of total cures. It is important to explore the portal and splenic veins for evidence of sclerosis and obstruction and to repair any pathology found, if possible. Occasionally following splenectomy the platelets will rise to high levels, and a count above one million carries with it danger of intravascular clotting which should be guarded against by the use of heparin, x-ray and the avoidance of dehydration.

In recent years Doan has suggested what appears to be a refinement of the clinical picture just described. One syndrome is called primary splenic neutropenia and the other with more widespread involvement of the blood elements called primary splenic hematopenia. In both of these the spleen is enlarged, there is a hyperplastic bone marrow and there is cure with splenectomy. Fever, nausea, fatigue and left upper quadrant pain may coexist but are not necessary for the diagnosis. It appears to me that one cannot admit the existence of the non-cirrhotic phase of the previously described congestive splenomegaly, particularly that type in which the etiology is intrinsic in the spleen, and also subscribe to these two entities. This being the case the difference between the two appears to be primarily one of nomenclature.

The accompanying table and graph, together with the preceding report suffice to classify this case as congestive splenomegaly secondary to intrinsic factors in the spleen without much laboring of the point. The neutropenia and thrombocytopenia were particularly marked preoperatively. It is of interest that the cephalin flocculation of four plus preoperatively has gradually subsided to a value of two plus some weeks postoperatively. This may be taken as indirect evidence that some liver damage already existed prior to operation and that a reparative process has set in. The absence of any pathology in the splenic or portal veins and the absence of any demonstrable liver damage bodes well for the prognosis although a definite guarantee of cure cannot be given until an appreciable time has elapsed.

Dr. Gerald H. McAteer: Newer concepts of the hormonal influence of the spleen on the bone marrow and the circulating blood makes for clearer understanding of spleen physiology and possibly the indications for its surgical removal.

Although this organ is not usually classified with endocrine systems, evidence is accumulating that the spleen does produce hormones that have distant effects on other organs.

In the normal state both quantitative and qualitative effects are noted in the circulating blood and this harmony is not upset by removal of the normal spleen. However, under abnormal splenic influences bizarre blood pictures may ensue wherein all of the circulating elements may be de-

pressed, i.e. pancytopenia or the action may be selective effecting one or more of the circulatig elements; these would include anemia, neutropenia and/or thrombocytopenia alone or various combinations.

The above case represents hypersplenism with pancytopenia of a slowly progressive nature with an enlarged spleen that filled most of the left abdomen. The indications for splenectomy were obvious after a complete work up as was done in this case.

Damashek classifies the indications for surgery as follows:

1. Absolute:
   - A. Rupture.
   - B. Idiopathic thrombocytopenic purpura particularly if acute.
   - C. Congenital hemolytic jaundice of the spherocytic variety and if one or more crises have occurred.
   - D. Acute or subacute hemolytic anemia when medical measures fail and specific causes for hemolysis have been ruled out.
   - E. Tumors and cysts of the spleen.
2. Probable indications:
   - A. Certain cases of splenic neutropenia.
   - B. Mediterranean sickle cell anemia with unusual hemolysis.
   - C. Splenic disease with pancytopenia.
3. Possible Indications:
   Chronic congestive splenomegaly including cirrhosis of the liver particularly those with leukopenia and thrombocytopenia

Pre-operative Preparation

Frequent transfusions are done to bring the blood picture to as near normal as possible. Adequate attention must be paid to hydration and electrolyte balance. Vitamin K has value in preventing prothrombin deficiency. Lavage and deflation of stomach prevent expressing gastric contents into pharynx during operative manipulations. Enemata and deflation of colon permits these organs to be easily packed off without the trauma attendent to distended bowel.

Operation

The need for skilled anesthetist needs no elaboration here. A transverse incision running from lateral border rectus is preferred as affording best exposure. The rectus may be incised with impunity if desired.

If technical considerations permit after mobilizing the spleen, the splenic artery should be clamped first and the dissection of splenic attachments continued between forceps. This is in effect a transfusion through the still intact splenic vein at a time when it is probably most indicated. In the case described the total volume of the spleen decreased

about 25% in size following this procedure. Due regard for this additional circulating blood must be considered if a transfusion is being given simultaneously to prevent overloading the circulatory system. The splenic vein is ligated and the organ removed.

Strict hemostasis should be observed here because of the frequent association of portal hypertension, and all vessels carefully ligated.

This case was unusual in having 3 accessory spleens or hyperplastic hemolymph nodes along the course of the splenic vein. They were removed. It is considered that splenic function may be restored after splenectomy through hypertrophy of hemolymph nodes and accessory splenic tissue, hence a diligent search should be made for their presence.

Inspection of the portal system showed no evidence of old or recent disease involvement and the liver appeared normal. Closure was made layer to layer.

Prognosis in this case would appear excellent in view of the absence of portal system disease and normal appearing liver. The immediate postoperative thrombocyte overproduction was not unexpected; daily platelet counts showed a considerable rise as noted in the accompanying charts. The advisability of administering heparin to forestall the eventuality of a thrombosis due to the rising thrombocyte count was carefully considered; however, the platelet count rapidly returned to normal during the second week following splenectomy thus precluding the necessity of heparin administration. Some observers arbitrarily recommend heparin and dicoumarol following splenectomy if the resulting thrombocytosis exceeds one million platelets.

THE SIGNIFICANCE OF HISTOPLASMIN SENSITIVITY: STUDY OF 441 INDIVIDUALS OF PEDIATRIC AGE

R. W. Alman, M.D.
M. Opinsky, M.D.

Introduction

In a recent paper Palmer reported the results of testing 3105 nurses in Minneapolis and St. Paul, Minnesota; Kansas City, Missouri; Kansas City, Kansas; Detroit, Michigan; and Philadelphia, Pennsylvania. Results of the survey were interpreted as indicating that mild infection with Histoplasma capsulatum or an immunologically related organism is very common in widespread localities in the United States, and that it is probably the principal cause of non-tuberculous pulmonary calcification.

Palmer found among the 3105 nurses studied 711 or 22.9 percent showed a positive reaction to histoplasmin. However, great differences were found in the percentage of nurses reacting to the histoplasmin in the several cities. In Minneapolis and St. Paul, 6.3 percent gave a definite or doubtful reaction; in Philadelphia, 12.6 percent; in Detroit, 14.4 percent; in Kansas City, Kansas, 54.0 percent and in Kansas City, Missouri, 65.8 percent. These figures are not completely representative prevalence rates of reactors for the city or state, since geographical migration is an important factor to be considered. About one-fifth (21.4 percent) of the total group of 294 nurses with calcification had a positive tuberculin reaction. Among the remaining four-fifths of this group (231) who had a negative tuberculin test, 206 had a positive or doubtful histoplasmin reaction. Only 25 nurses (8.5 percent) of the 294 with calcification had a negative reaction to both histoplasmin and tuberculin. To bring these findings together, 91.5 percent of the group having pulmonary calcification reacted to tuberculin or histoplasmin or both; a greater part reacted to histoplasmin than to tuberculin. Further evidence in Palmer's study shows the following to be true. Among those reacting only to tuberculin, 10.4 percent showed pulmonary calcification, while among those reacting only to histoplasmin, 31.1 percent showed calcification. Among those reacting to both antigens, 34.1 percent showed calcification which is a higher incidence (as mght be expected) than among those reacting to either antigen alone. Among the large group that did not react to tuberculin or histoplasmin, a low rate of 1.2 percent with pulmonary calcification was found.

Present Investigation

The present study was undertaken in an effort to determine the age incidence and distribution of histoplasmin sensitivity among children

residing, for the most part, in the District of Columbia and surrounding area. This preliminary report is limited to the survey of 441 patients admitted to Children's Hospital for miscellaneous illnesses, and in the age group ranging from 5 days to 12 years. Two older children and a group of 38 adults also tested are not included in the series; it should be mentioned here that the results obtained in the older group are in accordance with previous investigation as to the general incidence of histoplasmin sensitivity among an adult population.

Method

Children studied were white and negro ward cases, of both sexes, and without reference to illness. The antigen used was supplied by Dr. Emmons of the U. S. Public Health Service. The 1:100 dilution was utilized, it having been determined that except in possible anergic states practically all sensitive individuals will react to this strength. One tenth cc. was injected intradermally into the flexor surface of the right forearm, and differentiated from the site of the concomitant tuberculin test by being circled with gentian violet. Injections were performed by nurses experienced in the technique of intradermal inoculation and were presumed to be uniform in character. All readings were done by the same person, to insure uniformity in interpretation. Positive reactions were arbitrarily considered to be those having an area of erythema or induration (the latter, especially, in the darker negro children) of 5 mm. or more in diameter, and were observed twenty-four and forty-eight hours after inoculation. A Mantoux tuberculin test was also performed routinely. All histoplasmin positive cases, regardless of tuberculin reaction, were sent to the x-ray department for chest roentgenograms, and the resulting films were scrutinized carefully for evidence of pulmonary pathology.

The majority of histoplasmin-negative cases had only a 3 mm. area of induration at the site of injection by the end of forty-eight hours. This was attributed to the irritant quality of the preparation, which caused a moderately severe burning sensation locally, while being injected.

Histoplasmin-Sensitive Cases

Significant data concerning the histoplasmin-positive cases are presented in Table 1. Reactions varied from 5 and 6 mm. areas of erythema and induration to 30 mm. areas of erythema and induration. No positive reaction was so delayed that it did not become positive until after 24 hours.

It will be noted that these 16 cases constitute 3.6% of the total series. Of 2 older children and 38 adults tested (not included in this series) 10% were histoplasmin-sensitive. This finding is mentioned only to point out the obvious fact that histoplasmin sensitivity is acquired. That more

adults than children are sensitive is of even greater significance, as will be indicated later.

The ratio of males to females is 9:7, equivalent to equal incidence in a series of this small number. The ratio of males to females in all patients was 225:216. There were 13 negroes to 3 whites, a 4.33:1 ratio; this ratio, among all patients, was 2.26:1. Though this discrepancy is rather large in

TABLE 1

CASE	RACE	SEX	AGE	HISTOPLASMIN (MM.)* 48 HOURS			DIAGNOSIS
				E	I	O.T.	
D. M.	C	F	10 m.	5	8	Neg.	Bronchopneumonia
T. R.	C	M	18 m.	12	14	Pos.	Tuberculosis?
W. W.	C	M	3 y.	5	6	Neg.	Cranial osteomyelitis; Brain abscess
C. R.	C	M	4 y.	10	14	Neg.	Malnutrition
E. M.	C	F	5 y.	10	12	Neg.	Upper resp. infection; febrile convulsion
B. C.	C	F	5 y.	15	20	Neg.	Rheumatic fever
C. S.	C	M	6 y.	10	12	Neg.	Upper resp. infection; febrile convulsion
U. C.	C	F	6 y.	5	6	Neg.	Rheumatic fever
L. C.	W	F	7 y.	10	10	Neg.	Osteomyelitis, tibia
G. R.	W	M	8 y.	15	15	Neg.	Muscular dystrophy
J. McJ.	C	M	9 y.	14	14	Pos.	Cellulitis of jaw; osteomyelitis?, mandible
I. C.	C	M	9 y.	20	20	Neg.	Rheumatic fever
F. B.	C	F	10 y.	8	12	Neg.	Rheumatic fever
R. R.	C	M	10 y.	20	20	Neg.	Influenza
A. R.	W	F	11 y.	30	30	Neg.	Upper resp. infection
J. J.	C	M	12 y.	8	10	Pos.	Otitis media

* E = erythema; I = induration (measured in millimeters); O.T. = old tuberculin.

spite of the small number of patients, the negro's greater exposure to all infections, due to his socioeconomic conditions, serves to negate the probability of primary racial susceptibility.

With 3 exceptions, all x-ray films showed parenchymal and hilar pulmonary calcification described as "apparently representative of a healed or healing primary complex." One of the 3 exceptions (T. R.) had been hospitalized for several months because of respiratory symptoms and rather indolent infiltrative lesions at the right base and hilus, not calcified, and first interpreted as tuberculosis. Inability to isolate the organism and the excellent clinical condition of the child later caused diagnoses of atypical bronchopneumonia and foreign body aspiration to be entertained; benign

pulmonary mycosis was not suggested. In a second exception (C. S.) only pronounced increase in bronchovascular markings was noted; and in the third exception (G. R.) no pulmonary pathology was evident. It is of interest to note that in the case of F. B., whose x-ray showed "perihilar infiltration and early calcification," the tuberculin test was negative, although an x-ray taken only 8 months previously had shown no pathology.

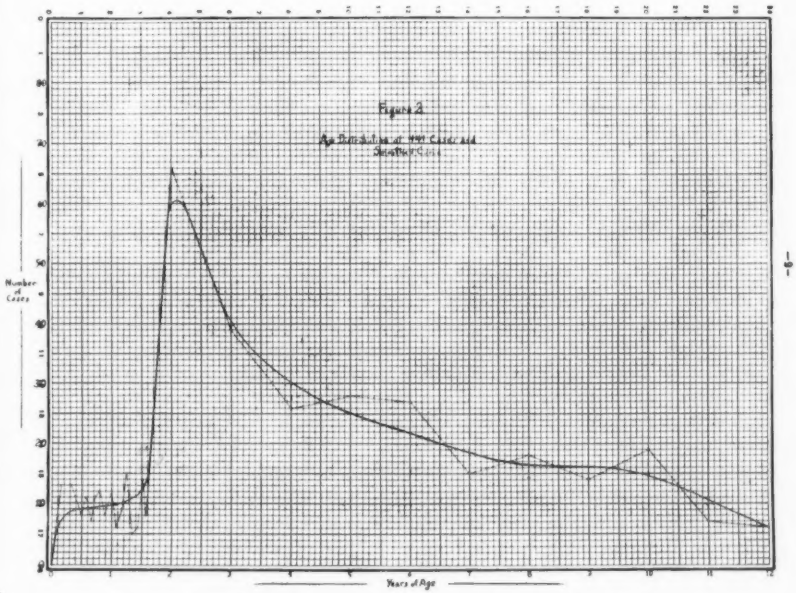

FIG. 2. Age Distribution of 441 Cases and Smoothed Curve

The high incidence of 4 cases of rheumatic fever, and 3 cases of proven or suspected osteomyelitis (a fourth case in a 14 year old child sensitive to both tuberculin and histoplasmin is not included in the series) can only be speculated at this time.

AGE DISTRIBUTION

For purposes of study and because a small series is exceedingly sensitive to single case variations, the age distribution curve of Fig. 2 has been expressed as the actual number of cases in each age group among the total series. Actual distribution should be indicated by the area under the part of the curve between whatever two ages are chosen as limits; and exact computation must be made by the individual reading the graph. However, be-

cause of the impracticability of recording ages of older children in terms of months, it was decided to permit only fourteen reference points to be placed on the curve: 0 (birth), the years numbered from one to 12 and the age 19 months. It is the almost universal custom to refer to the age of a child under 2 years either in months of age or as "two years old," if the second birthday is sufficiently close. Older children usually have their ages described according to the nearest furture birthday, if it is not more than 3 months away, or the nearest past birthday if not more than nine months past. Thus, children of 6 years 10 months, or 7 years 8 months, are usually loosely referred to as "seven years old." Therefore, it was arbitrarily decided to include all children between 20 months of age and "two and a half years" in the group of two-year-olds; younger children were considered to have had their ages accurately reported, and were so charted; older children were placed in groups of gross age designation, any fraction of a year having been ignored. The resulting graph was smoothed as well as practicable by the method of equal areas. The only finding worthy of note in Fig. 2 is that the largest group of cases is between 2 and 3 years of age.

The incidence of histoplasmin-sensitive individuals in each of the age groups of Fig. 3 (for determination of which incidence, it was necessary to collect the data from which Fig. 2 was derived) is expressed on a percent basis. Obviously, the greater the number of cases in the age group in which positive histoplasmin reactions occur (as noted by the height of the superimposed smoothed curve taken from Fig. 2), the greater is the accuracy of the percent figure in that age group, expressed by the position of the mark indicating histoplasmin sensitivity. In this connection, reference to the smoothed curve in Fig. 2 will show that of the 12 age groups, 7 are comprised of less than 20 individuals each. Consequently, it is somewhat surprising that the histoplasmin-positive distribution does not show far more variation from the "ideal curve" of Fig. 3 than it does.

The form of this "ideal curve" was determined by considering a hypothetical group of persons "negative" at birth, among whom a fixed proportion of the remaining "negatives" become "positive" by the end of each year, and none of whom dies. The mathematical expression for such a situation is $P = 100\left[\frac{(n-1)^2}{(1-n)}\right]$ where "P" is the percent of "positives" at any given year of age "a", and $1/n$ is the fraction of remaining "negatives" changing to "positive" each year. The curve of this equation was constructed for the value $n = 100$, since, under such circumstance, 40% of a group will be positive at the age of fifty years (approximately the finding of Emmons, et al. for this geographical area). This construction admittedly does not allow for skewing of the curve due to variations in incidence

in areas of previous residence, variations in individual exposure and suspectibility, and deaths. The "ideal curve" is presented solely as an approximation of what might be expected under ideal conditions.

Conclusions

The most important fact brought out by this study is that the incidence of histoplasmin sensitivity tends to increase with regular and rather rapid

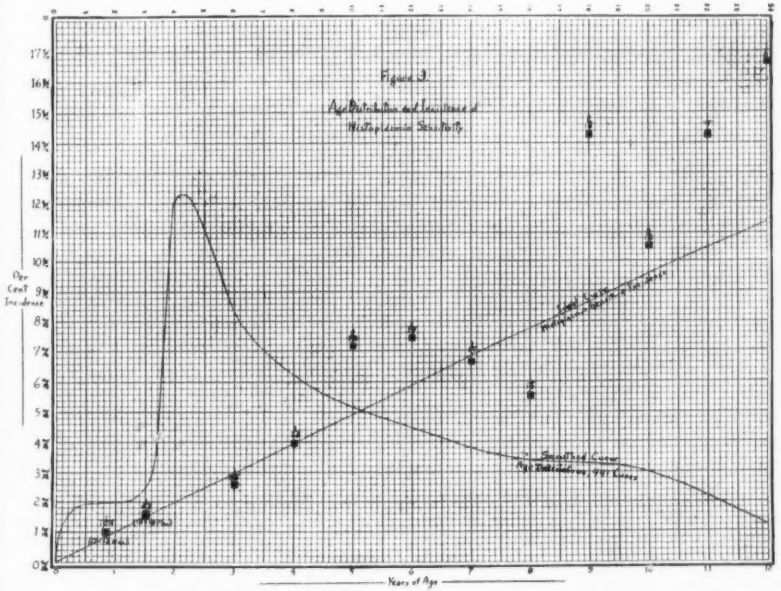

Fig. 3. Age Distribution and Incidence of Histoplasmin Sensitivity

progression with age. If the infection causing this situation were such as to result in a uniformly fatal disease, there would be no such progressive increase in numbers of sensitive persons, since other such sensitized persons would die at an equal rate, which would be constant and high. This is especially true of children, who succumb to many of the infections which the normal adult resists with ease, and in whom histoplasmin sensitivity appears rather early.

The following reasoning leads to the conclusion that the existence of a benign histoplasmosis, responsible for the positive histoplasmin test, is unlikely; no known disease has two, and only two, forms—one invariably fatal, the other invariably benign and nearly asymptomatic. Therefore,

a benign histoplasmosis should suggest an intermediate histoplasmosis; and enough liver, spleen and bone marrow biopsies, blood cultures, and blood films are examined in ilnesses difficult of diagnosis so that surely many non-fatal case of histoplasmosis should have been discovered, if this is the disease responsible for histoplasmin-sensitivity in upwards of ten percent of the population.

The only remaining logical supposition is that the great majority of histoplasmin reactions in man are not due to infection with H. capsulatum. The test itself has been directly proven to be non-specific. As a corollary to this hypothesis, it can be stated that pulmonary calcification in tuberculin-negative persons is probably due in the majority of cases to previous infection by one or more of various fungi, perhaps one of the Monilia—which very frequently cause mild infections in infants and children. It is pertinent to recall here that radiologists are now familiar with the picture of healed widespread pulmonary aspergillosis and moniliasis, once believed to be "healed miliary tuberculosis"; we feel that, until recent studies, they have been similarly misinterpreting many x-rays simulating the healed Ghon complex.

The small number of tuberculin-negative and histoplasmin negative cases with pulmonary calcification may have been without antigenic stimulus for so long a time that sensitivity has disappeared, though the original infection may have been either tuberculosis or one of the benign mycotic infections.

The only value of the histoplasmin test is as a non-specific antigen to demonstrate present or past sensitization by a benign mycotic infection. It is suggested that the incidence of histoplasmin sensitivity in persons known to have such benign mycotic infections—particularly, those due to Monilia (Candida) albicans—be compared with that of an unselected group.

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HYPERTELORISM

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K. R., a 19 month old white female, was admitted to the hospital on August 28, 1943 with the chief complaint of vomiting and "nervousness." The patient was an only child and was born after normal delivery with bilateral hare lip and cleft palate. The hare lip plastic repair was done in the first month of life and one month before admission an attempt was made to repair the cleft palate. Following the latter operation the baby had been vomiting intermittently about twice a day, had become very irritable and cried frequently. She had lost 6 lbs. during this period of time. There was no history of abnormalities or malformations in the background. The parents were 28 and 25 years of age respectively. The mother gave no history of sickness or infection during the gestation.

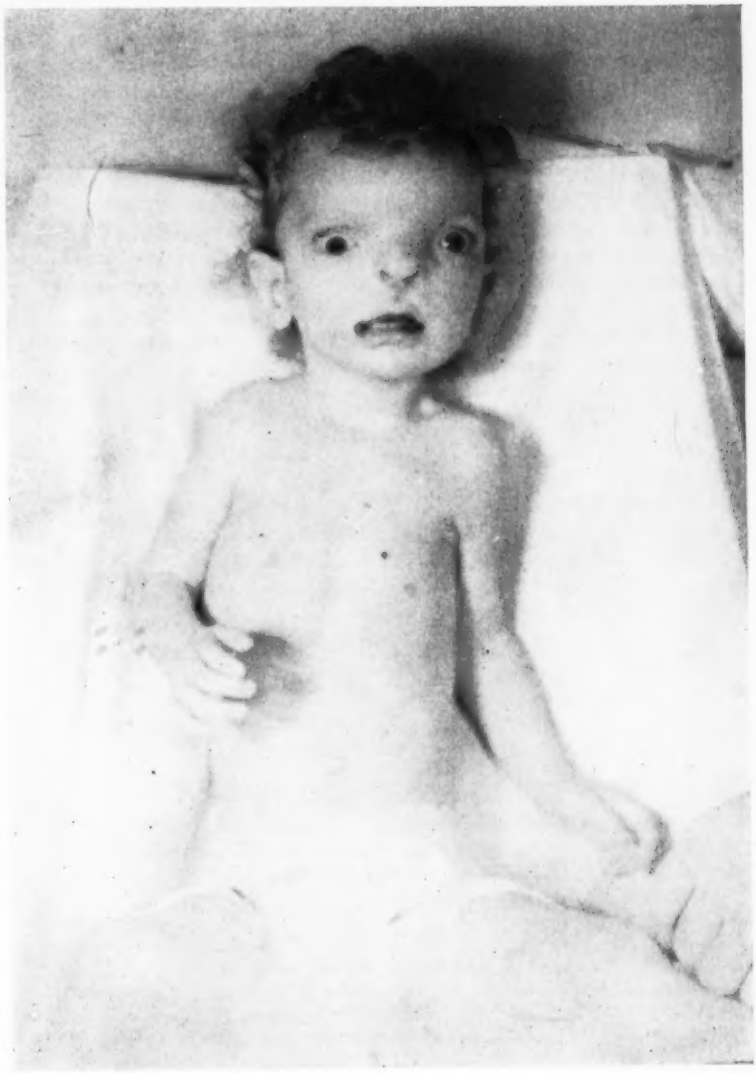
Physical examination presented a pathetically repulsive appearing child whose orbits were tremendously far set apart with probably no vision in the left eye. She could not focus her eyes, each being directed in a lateral oblique line. There was a partially repaired cleft palate and a repaired bilateral hare lip. The nose appeared widespread and misshapen. The trunk appeared extremely thin and wasted. The pelvis was very small and narrow. The rump-brown length was elongated and in association with her small hips accentuated the malformation of her head producing a "wolf-like" expression and appearance. The extremities appeared wasted.

Impression upon admission was hypertelorism, cleft palate and repaired hare lip. The child ran an irregular fever ranging between 100° and 101.8° until the 6th hospital day at which time she developed nuchal rigidity. Spinal fluid examination showed 2,000 cells and numerous organisms having the morphology of H. influenza. She was given sodium sulfadiazine for 4 days without an significant effect and on the 10th hospital day her temperature reached 105.2 and she expired. Autopsy permission was refused.

Discussion

Ocular hypertelorism is a congenital cranial facial deformity of rather rare occurrence that was first described by Greig[1] in 1924. Since that time approximately 30 cases have been reported in the literature and in only two of these was the association with cleft palate and hare lip noted.[2]

Berliner and Gartner[3] define this condition as a congenital anomaly of the skull characterized by a widespread separation of the orbits causing the eyes to be too far apart. The large interpupillary distance is exaggerated by a divergent squint in most cases. The anomaly produces an animal



Ocular Hypertelorism

appearance of the face. Mild degrees of this condition are common and since no symptoms are produced are often overlooked and if observed are regarded as a familial bone structure feature which is quite often true. In marked cases, however, mental deficiency is the rule and the association with various other anomalies has been the subject of nearly all the papers written on this condition in recent years.

Rubens[4] reported 2 cases of hypertelorism with cleidocranial dysostosis and was able to trace the family history back for 5 generations. Cowan and Silberman[5] commented on its appearance in 2 of 3 siblings, the father having a similar appearance. Posner and Platt[6] reported a case of ocular hypertelorism with cleft palate in association with a giant cell tumor. Callister reported a case with facies bovinia.[2]

Other deformities that have been seen in association are syndactylism, cryptorchidism, acrocyanosis, high palate, fragillitus ossium, nasal malformations, dental abnormalities and occasionally an association with congenital syphilis.

Little is known about the cause of this abnormal genetic variation. According to Grieg,[1] "In this anomaly about the third month of fetal life the lesser wings increase greatly in width so much so that they may be equal to or even larger than the greater sphenoidal wings. The lesser wings of the sphenoid form the posterior part of the root of the orbit. Thus due to the enlargement and premature ossification of the lesser wings, the fetal lateral deviation of the orbit remains fixed."

The various other deformities seen with hypertelorism would indicate that multiple mutations are quite commonly associated with this one. There has been no evidence presented that would associate these deformities with any maternal disease and the etologic background remains obscure.

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RITTER'S DISEASE (DERMATITIS EXFOLIATIVA NEONATORUM): REPORT OF A CASE

Case Report No. 78

Dr. Clifford J. Tichenor W. F. 46–8824

Attention is directed to the condition known as Ritter's Disease or Dermatitis Exfoliativa Neonatorum because there are a few pertinent facts about bullous disease in the infant that warrant discussion. It is difficult to separate this disease entity from pemphigus neonatorum, epidermolysis bullosum congenita and Leiner's Disease (Erythroderma Desquamativum) since there is apparent overlapping in both the clinical and pathological manifestations.

Case Report

W. F., a white male infant, age six days, was brought to our isolation wards from a nursery of a local hospital because of extensive areas of desquamation over the entire body. A small local area of hyperemia and desquamation had appeared near the region of one eye twenty-four hours prior to admission and had rapidly spread to involve all of the body.

Delivery was at full term, spontaneous, and there were no neonatal difficulties. The birth weight was 2160 grams and the inital and subequent cries were weak. Activity had been good on stimulation however, and there was no apnea, cyanosis, anemia or jaundice. The body temperature had been stable. No medications, locally or parenterally had been used and nothing other than breast milk had been taken by mouth. Family history for similar skin lesions was said to be negative and consanguinity of the parents was ruled out. The maternal serology for lues was negative.

The temperature on admission was 98.6F and the pulse rate was 134.

Physical examination when the patient was first seen revealed a small, fairly well developed and well nourished new born infant appearing acutely and seriously ill and presenting large areas of denuded skin on the face and thorax, with undue wrinkling of the remaining skin preparatory to peeling over the entire body. The extensive desquamation also involved the buttocks, palms and soles. The left eye was swollen and tightly closed, but there was no evidence of any purulent discharge. One large bleb filled with straw colored fluid remained over the right shoulder area. Nikolsky's sign (easy removal by friction of undenuded skin) was strongly positive. No lesions were noted in the mouth or at the external sites of other mucous membranes. The cry was feeble.

Laboratory findings were minimal. A dark field examination of aspirated fluid from a bleb revealed no Treponema pallidum. Culture of

this fluid grew hemolytic staphylococcus albus. Roentgenological examination of the long bones of the upper and lower extremities revealed only the absence of any ossification centers for the carpal bones.

Penicillin in the dosage of 40,000 units every three hours was given intramuscularly, the total dosage administered by this route being 1,460,000. Supportive measures included 130 cc. of plasma given in divided doses of 40 to 50 cc. intravenously, and one hypodermocylysis of 50 cc. of 5% glucose in saline. Locally, sterile mineral oil was applied to the raw skin surface as an emollient.

The temperature, which was stable at 97–98°F during the first four hospital days, rose to 101–102° during the 5th, 6th and 7th days and then returned to a normal level. The weight loss was 240 grams in one week, but then began a steady increment gain. The average fluid intake by mouth was 14 ounces of formula and 3 to 5 ounces of sterile water. Vomiting was negligible and there was an average of 4 to 6 soft well formed yellow stools daily. At the end of one week the infant was progressing satisfactorily and the large denuded, reddened, dry areas appeared to be healing. Penicillin was discontinued at this time. On the ninth hospital day the temperature rose to 103°F and it became evident that a cellulitis of face was developing. Concurrently harsh rales were discovered on the chest examination. The temperature remained elevated and respiratory embarrasment became a prominent symptom. Penicillin was again begun on the twelfth day, but the course was now rapidly downhill, the infant expiring on the thirteenth day after admission.

Necropsy was performed and demonstrated multiple lung abscesses, pyodermia with generalized desquamation and cellulitis of the face. Hearts blood culture grew hemolytic staphyloccus albus and E. coli. Culture and smear of the lung abscesses grew only Pseudomonas aeroginosa. Culture and smear was negative for any acid fast bacilli.

Discussion

Ritter's disease is said to develop in the first few weeks of life, usually beginning as a localized hyperemia on the face and spreading rapidly to involve the entire body. Characteristically there is marked wrinkling of the skin and sheetlike desquamation leaving extensive red denuded areas of corium. Nikolsky's sign is positive and quite characteristic. Fever is usually absent or only slightly elevated. With the advent of the sulfonamides, penicillin and supportive transfusions and parenteral fluids, this usually fatal disease now has a mortality of about 50%.

Leiner's disease usually appears first on the buttocks and gluteal folds and Nikolsky's sign is absent. Seborrhea of the scalp is often an associated feature.

Pemphigus neonatorum is a term reserved for superficial bullous lesions of the entire body, but not involving the palms and soles. Constitutional symptoms are usually marked. The bullae tend to develop in crops, each bulla varying in size from a pea to a hen's egg, being tense wih clear albuminous serum which becomes turbid, purulent, and occasionally hemorrhagic. The bulla is characterized by having at first no ring of erythema round its base. The fluid is either absorbed with formation of crusts, or the blebs burst, leaving a raw surface on which new epidermis soon develops. Any part of the skin may be affected, as well as the mucous membranes of the mouth, nose, throat, vulva and conjuctivae. Each bulla lasts a few days. The outlook is grave. In P. foliaceus the bullae are very thin and flaccid and rupture early; but the epidermis, instead of reforming, continues to peel off with large areas of red, raw, exuding surface being exposed, with the epidermis folded at the margins. This is a slowly extending process, however, before the entire body is involved.

The other bullous diseases must be passed in review. In children, bullous impetigo affects chiefly the face and has characteristic golden-yellow crusts; the bullous syphilide is seen in infants chiefly on the palms and soles. Serology and x-ray examination of the long bones are useful when there is a questionable etiology. Epidermolysis Bullosa is a very rare congenital disease in which slight traumatism causes the formation of bullae. It usually runs in families. The bullae appear on parts exposed to friction or pressure, and even the nails and scalp may be affected. Lesions are usually present on the mucous membrane of the mouth. An elevated basal metabolic rate is said by some to be present in this disease. The course is characterized by periods of exacerbation and remission, summer being the most unfavorable season. Nikolsky's sign is highly positive. Skin biopsy reveals separation of the epidermis from the underlying tissue with only slight inflammatory reaction and loss of elastic tissue. This disease is also present at birth or shortly thereafter. Although the bullae may occur anywhere on the body, the sites of predilection are the fingers, toes, knuckles, elbows and ankles. The etiology remains obscure although heredity appears to play an important rôle.

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ERYTHEMA MULTIFORMA BULLOSUM (STEVENS JOHNSON DISEASE)

Dr. Joseph Dugan

D. J., a 10 year old white male, was admitted to the Children's Hospital May 3, 1946 because of a generalized eruption of five days duration and ulcerations of the mouth. The condition began eight days prior to admission as a "cold sore" in his mouth. Three days later the eruption appeared on his face, successively involving the arms, trunk and legs. The child complained of pruritus, anorexia, malaise, vague abdominal aching and transient pain in the left knee. On April 29, 1946 a private physician administered oral penicillin which shortly thereafter was followed by six episodes of vomiting. The vomitus consisted of food and mucus. The physician then prescribed sulfadiazine but the condition progressed with the child becoming constipated and refusing to take anything but fluids by mouth. One day prior to admission he had a moderately profuse nosebleed.

The review of systems was non-contributory and the family history irrelevant. The past medical history revealed that the child had the same condition six months previous to the present hospitalization.

Physical examination revealed numerous erythematous and violaceous multiform lesions some of which were vesicular, others bullous covering the face and entire body. The scalp was free of involvement but there were ulcerations of the mouth and pharynx and mild injection of the conjunctivae. There was a generalized lymphadenopathy and the rest of the physical examination was essentially negative. Urinalysis revealed no albumin and a hemogram was within normal limits.

On admission sulfadiazine was discontinued and his treatment consisted of a soft diet, fluids, ascorbic acid 50 mgm daily, vitamin B complex 1 cc subcutaneously three times weekly, calamine lotion to the lesions on the body and 2 % aqueous gentian violet to the lesions in the mouth. His temperature ranged between 98° and 103° and on the ninth hospital day he complained of a stiff neck. Lumbar puncture revealed a normal spinal fluid but sulfadiazine grains 15 every four hours was given. His temperature gradually returned to normal, the lesions faded within 24 days and he was discharged from the hospital on the sixteenth day. He had gained two pounds during his hospital stay and a follow-up in the skin clinic one week and one month afterwards showed the child to have remained completely well.

Discussion

Dr. Paul Doolan: Erythema Multiforma Bullosum variously known as Stevens-Johnson Disease, Ectodermosa Erosiva Pluriorificialis, Dermato-

Erythema Multiforma Bullosum

Stomatitis (Baader) and Erythema Exudativum Multiforme with Ophthalmia and Stomatitis is at present a clinical syndrome which remains in need of proper classification and a more complete elucidation. Is it but one of the many members of the erythema family, is it related in any way to Rheumatic fever; or is it a distinct clinical entity in itself? Is the fundamental etiologic factor of an allergic or toxic nature?

The classical clinical description of the syndrome would be somewhat in the nature of the following. A two to sixteen year old male sometime during the spring or fall seasons is stricken with an acute onset of fever, malaise, headache and general toxicity. The sequence that follows is that simultaneously or within twenty-four to seventy-two hours there appears a crop of oval, non-pruritic, erythematous, multiforme, sometimes irislike and sometimes serpiginous macules varying from 0.5 to 6 cm. in their longest diameter and having no areolae. In a few days the macules become papular and acquire a violaceous hue. Some of the larger lesions may have a yellow, dry, necrotic center but there are no bullae or pustules. The face, trunk, upper and lower extremities are involved while the scalp remains lesion free.

At approximately the same time the patient complains about soreness of of the oral mucous membranes which appear erythematous and may be studded with vesicles or bullae. Later the bullae rupture causing extensive areas of erosions which in turn become covered by a friable whitish psuedomembrane. The lips, gums and tongue may be edematous and hemorrhagic crusts form over the erosions on the lips. The palatal, tracheal, bronchial and even bronchiolar mucous membranes, less commonly, may be involved resulting in the production of a copious and tenacious sanguinopurulent sputum which is raised with difficulty. So also may it result in the production of severe dyspnea or bronchopneumonia. In like manner similar lesions involve other exposed mucosae such as that of the nose, anus, vagina as well as in the meatus of the penis.

The most alarming feature of the disease is the ocular involvement. Duke-Elder classified the eye lesions into three types, an excellent discussion of which has been given by Koke[11].

i. Catarrhal form—a mild conjunctivitis which subsides simultaneously with the eruption and leaves no scars.
ii. Purulent form—an extreme conjunctival chemosis wherein corneal ulceration and perforation are not uncommon.
iii. Psuedomembranous form—the bulbar and/or palpebral conjunctiva are covered by psuedomembranes. Symblepharon occurs when the process becomes severe. Corneal involvement is almost invariable and usually results in ulceration with perforation or permanent diffuse opacification. Recurrences are common.

The condition has now attained its fastigium. The child has a fever of 102–105°, he is prostrate, toxic, and may complain of transient joint pains. This status is usually maintained only for a matter of days and then the patient begins to improve. During the third week begins a resolution of the older lesions with crusting and scaling. By the end of the sixth week the skin lesions have disappeared and there is no pitting or scaring. The ocular lesions may clear in a matter of 5 to 9 days or with the more serious forms recurrences may continue for years.

Variations from the above commonly occur for the disease may appear at ages over 16 years, it may affect females and the ocular or oral manifestations may precede the cutaneous lesions which in turn may be bullous rather than maculo-papular. The lesions may be pruritic, confined to the nose, mouth and eyes and the entire condition may be recurrent. The laboratory findings have been at even greater variance. No constancy has been found with regard to the CBC or percentage of eosinophils. Urinalysis may show a transient albuminuria but the blood cultures are uniformly negative. A variety of bacteria have been cultured from the different lesions, Staphylococcus aureus most commonly. Biopsy of one of the skin lesions revealed no specific information concerning an etiologic agent and inclusion bodies could not be demonstrated.

The differential diagnosis is most commonly concerned with one of the following three eruptions:

i. Pemphigus vulgaris whose onset is less abrupt, occurs in an older age group and pursues a different course.
ii. The human form of foot and mouth disease which is characterized by swelling and redness around the nails of the hands and feet with desquamation of the site of vesicles on the fingers and toes. Guinea pig inoculations may, however, be needed to establish the diagnosis.
iii. Toxic eruptions due to drugs and foods wherein the history, disposition of the lesions and the course rules it out in one case, the absence of severe gastrointestinal symptomatology in the other.

The treatment of choice is penicillin given parenterally for its systemic effect as well as applied topically to the ocular lesions. Sulfadiazine may be given orally while numerous antiseptic and analgesic preparations have been used on the cutaneous lesions. The patient should be made as comfortable as possible during the fastigium of the illness and his nutrition should be maintained.

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